the evidence for an association between indoor exposures and asthma and allergy. Medline and Embase were searched for relevant publications (1966 - 2005) by combining terms for exposures, indoor locations and appropriate health outcomes. Literature was reviewed according to Health Technology Assessment principles. Data when found suitable were extracted and combined in meta-analyses. The literature search yielded 11,641 publications, 2,175 abstracts were reviewed and 1,080 publications retrieved for full text assessment. Studies with a randomised, controlled, cohort or case-control design that provided both exposure data and health effect data were included. In the final assessment 362 relevant publications were included: 169 on allergen exposure, 141 on environmental tobacco smoke exposure, and 95 studies on dampness or chemical exposures. Environmental tobacco smoke and dampness and mould were found to be associated with increased risk of asthmatic symptoms, anti-mite interventions seemed to provide little benefit (preliminary), and pet exposure seemed to have little effect (preliminary). The publications were heterogeneous and often difficult to combine. Many studies were too small and had obvious methodological weaknesses.

879 INCORPORATING HAZARD IDENTIFICATION AND RISK ASSESSMENT INTO AN OCCUPATIONAL HEALTH AND SAFETY PROGRAM FOR ANIMAL RESEARCH

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Assessing risks to personnel involved with chemical exposure studies in animals and effectively communicating warning and safety information are critical components of an occupational health and safety program. In 2003, the University of Pittsburgh Department of Environmental Health and Safety (EHS) initiated internal development of a system to integrate investigator registration, hazard identification and risk communication. The system utilizes an EHS registration workbook to gather information about chemicals or drugs proposed for use. The workbook is a Microsoft Excel© spreadsheet completed in conjunction with an Institutional Animal Care and Use Committee (IACUC) protocol application. EHS identifies the chemical hazards and the risks associated with usage on each project, including dose, exposure route, size/length of study and potential for excretion of hazardous metabolites. EHS prepares a risk assessment document summarizing the hazards and providing recommendations for conducting the project safely, including engineering controls, personal protective equipment, work practices, signage/labeling, and bedding/waste disposal. EHS created a database to store the imported registration information, automatically populate sections of the risk assessment, and contain a standard phrase library for each chemical to ensure consistency in the warning statements and safety recommendations. The risk assessment also covers the use of biological materials and physical hazards, and identifies medical surveillance and training requirements for personnel. Since January 2004, EHS has prepared more than 800 risk assessments for IACUC protocols covering over 870 hazardous chemicals and drugs. The integrated system has proven to be very efficient for collecting information on large numbers of protocols and the risk assessment has been an excellent tool for communicating hazard warnings and safety recommendations to the investigator and laboratory and animal care staff, while also ensuring compliance with medical surveillance and training requirements.

880 PROCESSES TO MINIMIZE GENOTOXIC IMPURITIES IN PRODUCTION OF A NEW DRUG SUBSTANCE

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This report describes the process used by Eli Lilly and Company to minimize genotoxic impurities in production of a new drug substance. The report also quantifies the risks of exposure to these trace impurities. The upper limit is determined by safety, while production process controls and analytical detection procedures can result in lower levels. Safety evaluations limit impurities to a threshold for de minimis effects (e.g. threshold of toxicological concern - TTC). There is a high probability that a 10-5 cancer risk will not be exceeded if exposure to the genotoxic impurity is no more than the TTC. This probability is improved if chemicals with structural similarities to the most highly potent genotoxic carcinogens are avoided. Our results show there is a low probability that multiple genotoxic impurities each controlled to the TTC would result in a significant increase in cancer risk. The TTC protects for almost all of the genotoxic compounds that could be carcinogens. Our results show oncogenicity studies with the drug substance could detect 7-26% of the most potent carcinogenic impurities not controlled by the TTC. Therefore, avoiding production chemicals with structural similarities to the most potent genotoxic carcinogens, controlling other genotoxic impurities to the TTC, and completing oncogenicity studies with the drug substance are important processes to minimize the risk from exposure to trace levels of genotoxic production chemicals that might carry through to the drug substance.

881 A DECISION TREE INCORPORATING VAPOR INTRUSION INTO SCREENING RISK ASSESSMENTS OF HAZARDOUS WASTE SITES

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Over the last decade, California has evolved a process for screening level risk assessments at Federal Facilities, using US EPA Region 9 Preliminary Remedial Goals (PRGs) supplemented with CAL-modified PRGs reflecting California-derived toxicity criteria where appropriate. With increasing recognition of the importance of vapor intrusion into indoor air, we developed a decision tree approach to incorporate that exposure pathway. The Decision Tree accounts for contaminants in soil (ingestion, dermal absorption, inhalation of particles and vapors) and groundwater (ingestion and inhalation of vapors). Vapor intrusion is estimated on a site-specific basis using the Johnson and Ettinger model. Potential migration of contaminants from soil to groundwater can be estimated using US EPA soil screening levels. The utility of the Decision Tree approach was demonstrated at two test Sites. At both sites, the use of PRGs alone led to the conclusion that risks are minimal and the site could be eliminated as a concern. Risk assessment of all exposure pathways, including vapor intrusion into indoor air, yielded incremental risk estimates of 2E-3 for Site A and 4E-4 for Site B. Most (100% at Site A and 95% at Site B) of the risk estimate was from the vapor intrusion pathway. The Decision Tree approach is flexible, cost- and time-effective, and accounts for the vapor intrusion pathway. It evaluates total, incremental and background risks for both residential and industrial scenarios. The approach also provides a transition to a more site-specific (baseline) evaluation when a site does not meet the requirements for a screening level assessment. Additional pathways, such as home-grown produce consumption, may necessitate a baseline risk assessment. If ecological receptors need to be addressed, a separate ecological assessment is required.

882 EVALUATION OF THE RD_{50} FOR DETERMINING ACCEPTABLE LEVELS OF EXPOSURE TO AIRBORNE SENSORY IRRITANTS

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The RD_{50} (exposure concentration capable of producing a 50% respiratory rate decrease in male mice) has been used to evaluate airborne chemicals for their sensory irritation effects and has become an ASTM standard. Past studies have shown good correlations between the predicted levels from the RD_{50} values to the Threshold Limit Values (TLVs) established for the workplace. We investigated the application of the RD_{50} values in establishing exposure guidelines for the general public by comparing RD_{50} values to Lowest Observed Adverse Effect Levels (LOAELs) and acute Reference Exposure Levels (RELs). Current values for the RD_{50} were collected from the literature. These values were evaluated after selection for thoroughness in adhering to the ASTM procedures, e.g., species tested and exposure time. A common point of departure for guidance values is the LOAEL in humans. LOAELs for human sensory irritation were identified from the literature for comparison with RD_{50} values. RD_{50} values in mice and corresponding LOAELs in humans were identified for 24 chemicals. Using the same 24 chemicals we were able to affirm the correlation between RD_{50}s and TLVs. The relationship between RD_{50} values and LOAELs was log RD_{50} = 1.19 (log LOAEL) + 0.75 with a R^2 value of 0.81. This high correlation supports the use of this animal bioassay in establishing exposure limits for the general public. OEHHA had developed acute RELs to protect the general public including sensitive members. RD_{50} values in mice and corresponding RELs in humans were identified for 16 irritant chemicals. The relationship between RD_{50}s and RELs was log RD_{50} = 0.71 (log REL) + 2.55 with a R^2 value of 0.71. Consequently, the RD_{50} is a useful standardized method, which may be helpful in developing health protective values for workers and the general public.

883 CRITICAL REVIEW OF TRADITIONAL DRINKING WATER DEFAULTS FOR CHILDREN: IMPLICATIONS FOR RISK ASSESSMENTS

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When conducting risk assessments to safeguard children from chemical contaminants in drinking water, assessors have used the traditional default values of 1 liter per day water consumption for a 25 kg child, or 1 liter per day for a 10-kilogram child. However these decades-old consumption rates and weights do not appear to be relevant across the wide range of ages and developmental stages that comprise childhood. Recent legislation in California mandates that the Office of Environmental Health Hazard Assessment (OEHHA) use relevant exposure patterns for potentially susceptible populations in drinking water risk assessments. We derived drinking water consumption rates based on fluid intake rates and energy requirements of children, and we conducted an analysis on a recently published

(2004) evaluation of drinking water consumption and body weights in the U.S. from the Continuing Survey of Food Intakes by Individuals (CSFII, USDA 2000) as analyzed by the U.S. Environmental Protection Agency (US EPA). These analyses indicate that in many cases the traditional child-specific drinking water default values do not apply well to the current population of children in the U.S. In fact, the defaults underestimate water consumption rates on a bodyweight basis of very young children by 50 percent or more. Therefore, OEHHA is considering using the 90th or 95th percentile drinking water consumption rates from the US EPA analyses in our future risk analyses on children. Our presentation compares the CSFII derived water consumption rates to the default rates, as well as to rates derived by using other data. Using the proposed values in lieu of the defaults would sometimes substantially lower estimated health-protective values. Comments are invited on this approach, especially as it relates to protecting children.

884 THE ANALYSIS OF MIXED DISCRETE AND CONTINUOUS OUTCOMES USING DESIRABILITY FUNCTIONS

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Multiple types of outcomes are sometimes measured on each animal in toxicology dose-response experiments, and multiple analyses may increase the overall type I error. One approach to analyzing these outcomes in an integrated way is through the use of a composite score. We introduce the use of desirability functions as a way of deriving an overall score that uses information from each of the outcomes. This methodology is commonly used in the quality control engineering literature but has not been applied in toxicology. Desirability functions transform observed responses of any type to a 0-to-1 unitless scale, where smaller scores indicate less desirable responses (i.e., increased toxicity). The geometric mean is used to combine the scores and then a univariate statistical analysis can be performed. Compared to other composite scores discussed in the toxicology literature, this approach has two advantages. First, because of the mathematical nature of the geometric mean, the overall score is more sensitive to deviations from the typical response at each dose group. As a consequence, the estimate of the threshold is more sensitive to evidence of toxicity. Second, weights may be incorporated into the desirability function, making it possible to prioritize the importance of each endpoint. Using data from five outcomes (motor activity, brain and blood cholinesterase activity (ChE), gait score and tail pinch score: a combination of ordinal, count, and continuous responses) from a neurotoxicity experiment, we demonstrate the use of desirability functions to derive a composite score. We analyzed the overall score using a nonlinear exponential threshold model. Using the composite score the lowest dose tested exceeded the 95% confidence limits of the dose threshold. Further analyses indicated the composite score was sensitive to slight toxicity, mainly due to ChE inhibition. This research was partially supported by NIEHS training grant #T32 ES007334 and does not reflect U.S. EPA policy.

885 A DECISION-MAKING FRAMEWORK FOR SENSITIZATION SAFETY ASSESSMENT OF A NEW CHEMICAL

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A decision-making framework is proposed for use in the chemical sensitization assessment of new chemicals – ingredients or formulations. It is a useful guide on principles to be considered when faced with potential sensitization safety questions. Because of the wide variety of materials, progression through the tree and the final outcomes may be very different depending upon the exposure, type of materials, manufacturing practices and risk/benefit considerations. However, the basic approach must be consistent.

The decision-making framework of the chemical sensitization assessment of a new material includes the following key elements:

1. Material identification and characterization
2. Assessment of dermal and/or inhalation safety
3. Assessment of dermal and/or respiratory toxicity
4. Assessment of dermal and/or respiratory sensitization potential

As with any other safety assessment, both exposure and hazard must be considered. In working with this decision tree, it is important to realize that the order of the questions is somewhat arbitrary. In real life, several steps may occur simultaneously.

886 DEVELOPMENTAL TOXICITY AS AN ENDPOINT FOR HEALTH RISK ASSESSMENT

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Exposure to short-chain organic acids, such as 2-ethylhexanoic acid is associated with developmental toxicity in laboratory animals. Acceptable levels of 2-ethylhexanoic acid in drinking water were determined, since this chemical is leached from some products evaluated for certification under NSF/ANSI 61 (2004). Skeletal malformations and variations, dilated cranial ventricles, and clubfoot were observed in the offspring of rat dams orally exposed to 2-ethylhexanoic acid during pregnancy. Maternal deaths but no fetal effects were seen in rabbits. 2-Ethylhexanol produced delayed ossification in rats and no effects in mice, suggesting that the acid rather than the 2-ethylhexyl moiety is responsible for the developmental effects, consistent with the proposed mode of action of increasing fetal intracellular pH. Although developmental toxicity in mice was specific to the (R)-enantiomer, the stereospecificity was not incorporated into this risk assessment because potential drinking water exposure is to the optically inactive 1:1 racemic mixture. The weak relationship of the developmental toxicity and maternal zinc status in rats was accounted for through the intraspecies uncertainty factor, as the zinc status of the general population varies. Liver effects, such as increased absolute and/or relative weight, hepatocyte hypertrophy, and changes in cholesterol and triglyceride levels, were seen in several rodent toxicity studies. These hepatic effects were suggestive of peroxisome proliferation, thus given limited weight, as humans are resistant to this effect, while some rodents are highly susceptible. Based on the lack of human epidemiology data and of chronic studies of 2-ethylhexanoic acid in laboratory animals, the data are inadequate for an assessment of human carcinogenic potential. Positive in vivo but no in vivo genotoxicity data were identified. An oral Reference Dose of 0.3 mg/kg-day based on developmental toxicity was used to determine a long-term Total Allowable Concentration for 2-ethylhexanoic acid in drinking water of 2 mg/L and a Short-Term Exposure Level of 30 mg/L.

887 A RETROSPECTIVE ANALYSIS OF DEVELOPMENTAL STUDIES UTILIZED FOR THE RISK ASSESSMENT OF PESTICIDES

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Pesticides go through an extensive evaluation before entering the US market. This evaluation includes a comprehensive assessment of the toxicological profile of the pesticide including the potential to cause teratogenic or fetotoxic effects. For food use pesticides (i.e., pesticides whose use could result in residues on food or feed), prenatal developmental studies in two species are required (usually rat and rabbit). As interest mounts on the prospect of using fewer animals in toxicology studies, this retrospective analysis was undertaken to ascertain the utility of obtaining developmental studies in both species for risk assessment purposes. The analysis examines a variety of aspects involved in the assessment of developmental toxicity. Available databases were systematically reviewed and data extracted for information on the frequency of times a prenatal developmental study was used to establish a reference dose, the proportion of chemicals for which one species was more sensitive, and the nature of the effects noted in each species. Three hundred and twelve food use pesticides were included in this analysis. Developmental toxicity endpoints from either species were used to establish acute reference doses (aRfDs) for approximately 44% of the food use chemicals. The rabbit prenatal developmental toxicity study was used for establishing an aRfD for 19% of these chemicals, while the rat was used for approximately 24% of them suggesting a comparable sensitivity between species. However, this pattern is not reflected in the overall analysis since the effect level (LOAEL) for the prenatal developmental rabbit study was lower than the rat for 60% of all food use chemicals. The nature of the effects observed in the pre-natal development studies in either species was comparable. The most common effects were decreased fetal weight, delays in ossification, and post-implantation loss. This abstract does not necessarily reflect the views or policy of the USEPA.

888 PRELIMINARY VALIDATION STUDIES OF BCO-P

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The Bovine Corneal Opacity and Permeability Assay (BCP-P assay) has been accepted by the EU national coordinators at their 28th meeting as an alternative to the Draize rabbit eye irritation test and is used to classify a chemical as irritant (R41). The BCO-P assay may be routinely used for assessment of safety and as a test to classify and label chemicals as "severely irritating to the eyes". This organotypic assay is considered acceptable by the national authorities where a positive result in respect to severe irritancy is obtained. In this case no further animal testing is necessary. Normally in the BCO-P assay the bovine eyes are collected as fresh as possible after slaughter from an abattoir. The corneas are isolated shortly and the tests are performed as soon as possible (no longer than 12 hours). In order to optimize the test conditions, we have performed some validation studies to estimate the differences of the test results between applying fresh bovine eyes and using eyes which are preserved in MEDIUM 199 Modified supplemented with Dextran. We have also compared the BCO-P results, in which the corneas from the animals in different ages were used. In the validation studies three positive control substances, 2-ethoxyethanol, imidazol (20%) and benzalkoniumchlorid, have been tested for various treatment times. The validation studies are useful for further optimizing the BCO-P test conditions and increasing the reliability of this metho